Remarks/Arguments

Claims 16 and 18-27 are pending. Claim 17 is canceled without prejudice. Claims 25 and 26 were withdrawn by the Examiner as directed to an invention distinct from the elected invention. Claim 27 is new. Accordingly, claims 16, 18-24, and 27 are under consideration.

In the December 11, 2009 Office Action, the Examiner asserted that claim 16 was incomplete for omitting essential steps. In particular, the Examiner asserted that there was no step describing how the characteristic of the small molecule (that it does not bind to non-IRS2 proteins in the absence of IRS2) was determined. In Applicants' May 12, 2010 Amendment, a clause reciting that the small molecule cannot bind to non-IRS2 proteins in the absence of IRS2 was inserted into step (b) of claim 16. In the June 7, 2010 Advisory Action, the Examiner asserted that what was intended by the Applicant as a characterization of the small molecule was rather a characteristic measured by the claimed assay method. As discussed below, the clause recognizing the inability of the compound to bind to non-IRS2 proteins in the absence of IRS2 has now been removed.

1. Rejections under 35 U.S.C. § 112, second paragraph

Claims 16 and 18-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 18, which recited "protein of interest," was rejected for insufficient antecedent basis. Claim 18 has now been amended to recite "insulin receptor substrate 2 (IRS2)." Claims 19-23, which recited "host cell," were rejected for insufficient antecedent basis. Claims 19-20 and 22-23, which relate to a host cell into which an IRS2 nucleic acid has been introduced, have now been amended to recite "test cell." Claim 21, which relates to the level of expression of IRS2 in the control cell of claim 16, has now been amended to recite "insulin receptor substrate 2 (IRS2)" and "control cell." Applicants respectfully request that the rejection be withdrawn.

Claims 16 was rejected as incomplete for omitting an essential step because there is not determination of the characteristic "wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2." The Applicant respectfully suggests that claim 16 is complete as presented. Claim 16 recites a method of determining whether a small molecule is an activator or an inhibitor of insulin receptor substrate 2 (IRS2). Absence of binding to non-IRS2 proteins

in the absence of IRS2 is not a characteristic that must be measured or confirmed, but rather an inherent characteristic of a small molecule that is identified by the claimed invention.

More particularly, according to the method recited by claim 16, a test cell is provided which overproduces IRS2 and exhibits an increase of an IRS2-binding protein to IRS2, relative to a control cell which produces IRS2 at a lower level, or does not produce the IRS2 protein at all. Compared to a control cell, the test cell has increased sensitivity to a compound that binds to and activates or inhibits the IRS2 - IRS2-binding protein complex, relative to a compound that binds to an IRS2-binding protein in the absence of IRS2 or otherwise modulates non-IRS2 components of the IRS2 signalling cascade. Thus, the alleged missing step is inherent in the claimed method.

2. Rejection under 35 U.S.C. § 102

Claim 17 was rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,858,701. The rejection is moot in view of the cancelation of Claim 17.

3. Rejection under 35 U.S.C. § 103

The Examiner has maintained the rejection of Claim 16 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,858,701 ("the '701 patent") in view of U.S. Patent No. 5,688,655 ("the '655 patent"). The Examiner has asserted that the only deficiency in the '701 patent is that it does not explicitly teach comparison of the results from a test population that over-express IRS2 to a control cell population that produce IRS2 at a lower level (or not at all). Applicants most respectfully but vigorously disagree. As discussed below, neither the '701 patent nor the '655 patent disclose or suggest the concept of linking a compound that binds to IRS2 with the ability of the compound to modulate a defined cellular activity correlated with IRS2 but not (previously) demonstrated to be modulated by compounds that bind to IRS2.

More particularly, and in view of the Examiner's remarks in the Advisory Action regarding what is taught by the '701 patent at col. 6, lines 62 through col. 7, line 10, while the '701 patent teaches a method of determining whether a compound promotes or inhibits binding of an IRS2-binding protein to IRS2, the method involves detecting the formation of a complex which includes the IRS-2 polypeptide and the IRS-2 binding ligand, and not "examining the test cell for modulation of an IRS2-mediated cellular signal," as recited in claim 16. The deficiency in the '701 patent is not just the lack of a comparison to control, but the assay method itself,

because the '701 patent only discloses testing the ability of a compound to induce complex formation. The '701 patent does not teach or suggest that that modulation of complex formation between IRS-2 and an IRS2-binding protein by a compound is a measure of the ability of the compound to modulate the activity by binding to the IRS2 complex. Also, the assay in the '701 patent is silent as to the expression level of IRS2 or any of the cellular components in the assay, with no teaching or suggestion that there would be any reason to compare cells that express different levels of IRS2 or any other cellular component in an assay that simply detects complex formation.

The Examiner has asserted that any deficiency in the '701 patent is remedied by the '655 patent, which teaches comparison between test and control. However, as already pointed out, the '701 patent lacks more than just a comparison with control. The '701 patent also lacks any teaching or suggestion that the ability of a compound to modulate complex formation between IRS2 and an IRS2 ligand is a measure of the ability of the compound to bind to and modulate the activity of the IRS2 complex.

The '655 patent does not remedy this deficiency because the '655 patent teaches only a relationship between expression of a protein-of-interest (*e.g.*, IRS2) and a phenotype that depends on the activity and level of expression of the protein-of-interest. The '655 patent is silent with regard to any protein that functions in a multi-protein complex.

It is by the methods of the present invention that one distinguishes between compounds that bind to and modulate IRS2 complex activity in the cell (see, e.g., paragraph 0032), versus compounds that either bind to an IRS2 complex but do not modulate its activity, or compounds that modulate the IRS2 signal transduction cascade in cells but do so by modifying the biological effects of *other* intracellular protein or non-protein targets in this pathway. By way of example, insulin would be an activator according to the '701 patent, but not the instant invention.

The Applicants point out that modulation of a target protein's activity by a compound may be direct (*i.e.*, the compound binds to and modulates the activity of a target protein) or indirect (*i.e.*, the compound binds not to the target protein complex but to another cellular component outside the complex to exert its effect). Distinguishing between direct and indirect modulation of a target protein is problematic with targets like IRS proteins, which are "docking" proteins. IRS proteins link the Insulin Receptor to other intracellular proteins in order to transduce the insulin signal, but have no intrinsic enzymatic activity that can be exploited.

Accordingly, the inventors have developed a pioneering approach to identifying compounds capable of directly modulating the function of IRS family members (and in particular IRS2). The approach is embraced by the definition of activator or inhibitor set forth in the application. In short, the instant method identifies small molecules that are direct modulators:

> By activator or inhibitor of IRS2 is meant a small molecule that binds to IRS2 alone and activates or inhibits the signaling function of IRS2, or a small molecule that binds to a complex comprising IRS2 and other cellular proteins and wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2.

Specification, paragraph [0032].

In this regard, the sections that the Examiner has cited in the '701 patent suggest that the term "IRS2 binding ligand" of the '701 patent is mistakenly being equated with "compound" of the instant invention. An IRS-2 binding ligand as discussed in the '701 patent refers to a naturally occurring protein ligand such as the Insulin Receptor ('701 patent, col. 6, lines 65-68). This is distinct from the small molecule test compound described in the instant application. As explicitly stated in column 7, lines 5-10 of the '701 patent:

> In another aspect, the invention features a method for evaluating a compound for the ability to modulate (e.g., to inhibit or promote) the binding of an IRS polypeptide (preferably other than IRS-1), *e.g.*, an IRS-2 polypeptide, with an IRS-2 binding ligand, *e.g.*, a naturally occurring ligand, *e.g.*, the insulin receptor. In the case of an IRS-2 polypeptide the method includes: (i) combining an IRS-2 polypeptide, an IRS-2 binding ligand, *e.g.*, a protein, and a compound; and (ii) detecting the formation of a complex which includes the IRS-2 polypeptide and the IRS-2 binding ligand. Modulation of the formation of the complex in the presence of the compound (*e.g.*, as compared with formation in the absence of the compound) is indicative of a modulation of the interaction between an IRS-2 polypeptide and an IRS-2 binding ligand. Other IRS polypeptides (preferably other than IRS-1) can also be used in this method.

('701 patent, Col. 6, line 65 through column 7, line 10). This passage says nothing about the small molecule of the instant invention that binds to the IRS2 complex. Nor does it teach or suggest anything about modulating the function of the complex by a small molecule that binds to the complex.

Thus, the '701 patent remains silent (as it must) with respect to whether or not the compound that causes modulation of the interaction between the IRS2 polypeptide and the IRS2

binding ligand does so by binding to IRS2, the IRS2 binding ligand, another protein or non-protein species present in the assay mixture, or simply modifies the solvent system or chelates or otherwise interferes with necessary ionic components of the assay milieu such that the interaction between IRS2 and the IRS2 binding ligand is altered in some manner. The Applicants understood the limits of their prior methods when conceiving and reducing to practice the invention of the instant application, and worked together so as to overcome such prior limitations.

Also, it is pointed out that the '655 patent focuses on target proteins evoking responsive changes in cells when overproduced. The presence of the target protein in a cell causes an observable phenotype whose intensity is related to the level of the activity of the target protein in the cell (*i.e.*, the level of the protein and its specific activity in the presence of a modulator). In this regard, the Examiner has suggested, based on the '701 patent, that IRS2 overexpression results in increased proliferation when IL-4 is added and that this could be the basis for a screening method that identifies compounds that modulate IRS2 function. (Office Action at p. 14). To the contrary, such a method would not distinguish modulators that act on IRS2 (or a complex containing IRS2) from modulators that act on other cellular components. Further, one of ordinary skill in the art would recognize that the screening method disclosed in the '655 patent makes use of the intrinsic enzymatic activity of a cellular enzyme to evoke a phenotype that responds both to the level of the protein and the activity of a protein as modulated by activators or inhibitors that act on that protein to identify modulators of that protein. IRS2 does not have such an activity nor does it evoke such a phenotype.

Accordingly, the Applicants respectfully suggest that the references relied on by the Examiner neither disclose nor suggest the claimed invention, let alone the feasibility of such an approach. Accordingly, the Applicants believe that the subject matter of Claim 16 (and its dependent claims) is not obvious and respectfully requests that the rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, the Applicants believe that the claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned attorney if there are any questions or issues that the Examiner feels can be resolved in a telephone interview.

Respectfully submitted,
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